Amendments to the Specification

Page 1, under the Title, replace the paragraph under the heading "CROSS-REFERENCE TO RELATED APPLICATIONS" with the following:

- - This is a divisional of US Patent Application No. 09/807,802, filed November 21, 2001, now US Patent 6,759,237, issued July 6, 2004, which is a 35 USC 371 (national phase) of PCT/US99/25694, filed November 2, 1999, which claims the benefit of the priority of US Patent Application No. 60/107,114, filed November 5, 1998. - -

Page 4, lines 12-17, replace the paragraph in its entirety with the following amended paragraph:

FIGS. 1A-1~~C~~F illustrate the alignment of nucleotides of AAV-1 ~~{~~(SEQ ID NO: 1)~~}~~, AAV-2 ~~{~~(SEQ ID NO: 18)~~}~~ and AAV-6 ~~{~~(SEQ ID NO: 19)~~}~~. The alignment was done with MacVector 6.0. The full sequences of AAV-1 are shown in the top line. Nucleotides in AAV-2 and AAV-6 identical to AAV-1 are symbolized by "." and gaps by "-". Some of the conserved features among AAVs are marked in this figure. Note the 3' ITRs of AAV-1 and AAV-6 are shown in different orientations.

Page 6, lines 18-26, replace the paragraph in its entirety with the following amended paragraph:

The AAV-1 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 1 (FIGS. 1A-1~~C~~F), which consists of 4718 nucleotides. The AAV-1 nucleic acid sequences of the invention further encompass the strand which is complementary to SEQ ID NO: 1, as well as the RNA and cDNA sequences corresponding to SEQ ID NO: 1 and its complementary strand. Also included in the

nucleic acid sequences of the invention are natural variants and engineered modifications of SEQ ID NO: 1 and its complementary strand. Such modifications include, for example, labels which are known in the art, methylation, and substitution of one or more of the naturally occurring nucleotides with an analog.

Page 7, lines 20-30, to page 8, lines 1-6, replace the paragraph in its entirety with the following amended paragraph:

Also included within the invention are fragments of SEQ ID NO: 1, its complementary strand, cDNA and RNA complementary thereto. Suitable fragments are at least 15 nucleotides in length, and encompass functional fragments which are of biological interest. Certain of these fragments may be identified by reference to FIGS. 1A-1~~C~~F. Examples of particularly desirable functional fragments include the AAV-1 inverted terminal repeat (ITR) sequences of the invention. In contrast to the 145 nt ITRs of AAV-2, AAV-3, and AAV-4, the AAV-1 ITRs have been found to consist of only 143 nucleotides, yet advantageously are characterized by the T-shaped hairpin structure which is believed to be responsible for the ability of the AAV-2 ITRs to direct site-specific integration. In addition, AAV-1 is unique among other AAV serotypes, in that the 5' and 3' ITRs are identical. The full-length 5' ITR sequences of AAV-1 are provided at nucleotides 1-143 of SEQ ID NO: 1 (FIG. 1A) and the full-length 3' ITR sequences of AAV-1 are provided at nt 4576-4718 of SEQ ID NO: 1 (FIG. 1~~C~~F). One of skill in the art can readily utilize less than the full-length 5' and/or 3' ITR sequences for various purposes and may construct modified ITRs using conventional techniques, e.g., as described for AAV-2 ITRs in Samulski et al, Cell, 33:135-143 (1983).

Page 20, lines 18-26, replace the paragraph in its entirety with the following amended paragraph:

The entire AAV-1 genome was then determined by automatic sequencing and was found to be 4718 nucleotides in length (FIGS. 1A-1~~C~~F). For sequencing, an ABI 373 automatic sequencer as used to determine the sequences for all plasmids and PCR fragments related to this study using the FS dye chemistry. All sequences were confirmed by sequencing both plus and minus strands. These sequences were also confirmed by sequencing two independent clones of pAV-BM, pAV-BL and pAV-BR. Since the replicated form of AAV-1 DNA served as the template for sequence determination, these sequences were also confirmed by sequencing a series of PCR products using original AAV-1 seed stock as a template.

Page 21, lines 16-29, to page 22, lines 1-2, replace the paragraph in its entirety with the following amended paragraph:

Although the overall features of AAV terminal repeats are very much conserved, the total length of the AAV terminal repeat exhibits divergence. The terminal repeat of AAV-1 consists of 143 nucleotides while those of AAV-2, AAV-3, and AAV-4 are about 145 or 146 nucleotides. The loop region of AAV-1 ITR most closely resembles that of AAV-4 in that it also uses TCT instead of the TTT found in AAV-2 and AAV-3. The possibility of sequencing error was eliminated using restriction enzyme digestion, since these three nucleotides are part of the SacI site (gagctc; nt 69-74 of SEQ ID NO: 1). The p5 promoter region of AAV-1 shows more variations in nucleotide sequences with other AAV serotypes. However, it still maintains the critical regulatory elements. The two copies of YY1 ~~{~~(See, FIGS. 1A-1~~C~~F)~~}~~ sites seemed to be preserved in all known AAV serotypes, which have been shown to be involved in regulating AAV gene expression. In AAV-4, there are 56 additional nucleotides inserted between YY1 and E-box/USF site, while in AAV-1,

there are 26 additional nucleotides inserted before the E-box/USF site. The p19 promoter, p40 promoter and polyA can also be identified from the AAV-1 genome by analogy to known AAV serotypes, which are also highly conserved.

Page 22, lines 19-22, replace the paragraph in its entirety with the following amended paragraph:

The nucleotide sequences of AAV-1, obtained as described above, were compared with known AAV sequences, including AAV-2, AAV-4 and AAV-6 using DNA Star Megalign. This comparison revealed a stretch of 71 identical nucleotides shared by AAV-1, AAV-2 and AAV-6. See, FIGS. 1A-1~~C~~F.

Page 23, lines 16-27, replace the paragraph in its entirety with the following amended paragraph:

Although it is clear that AAV-6 is a hybrid of AAV-1 and AAV-2, AAV-6 has already exhibited divergence from either AAV-1 or AAV-2. There are two nucleotide differences between AAV-6 and AAV-2 in their first 450 nucleotides. There are about 1% differences between AAV-6 and AAV-1 in nucleotide levels from nucleotides 522 to the 3' end. There also exists a quite divergent region (nucleotide 4486-4593) between AAV-6 and AAV-1 (FIGS. 1A-1~~C~~F). This region does not encode any known proteins for AAVs. These differences in nucleotide sequences may suggest that AAV-6 and AAV-1 have gone through some evolution since the recombination took place. Another possible explanation is that there exists another variant of AAV-1 which has yet to be identified. So far, there is no evidence to rule out either possibility. It is still unknown if other hybrids (AAV-2 to AAV-4, etc.) existed in nature.